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Original article

N-Nitrosodimethylamine-Contaminated Valsartan and the Risk of Cancer

A Longitudinal Cohort Study Based on German Health Insurance Data

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Background: N-Nitrosodimethylamine (NDMA), classified as a probable human carcinogen, has been found as a contaminant in the antihypertensive drug valsartan. Potentially carcinogenic effects associated with the consumption of NDMA-contaminated valsartan have not yet been analyzed in large-scale cohort studies. We therefore carried out the study reported here to explore the association between NDMA-contaminated valsartan and the risk of cancer.

Methods: This cohort study was based on longitudinal routine data obtained from a large German statutory health insurance provider serving approximately 25 million insurees. The cohort comprised patients who had filled a prescription for valsartan in the period 2012–2017. The endpoint was an incident diagnosis of cancer. Hazard ratios (HR) for cancer in general and for certain specific types of cancer were calculated by means of Cox regression models with time-dependent variables and adjustment for potential confounders.

Results: A total of 780 871 persons who had filled a prescription for valsartan between 2012 and 2017 were included in the study. There was no association between exposure to NDMA-contaminated valsartan and the overall risk of cancer. A statistically significant association was found, however, between exposure to NDMA-contaminated valsartan and hepatic cancer (adjusted HR 1.16; 95% confidence interval [1.03; 1.31]).

Conclusion: These findings suggest that the consumption of NDMA-contaminated valsartan is associated with a slightly increased risk of hepatic cancer; no association was found with the risk of cancer overall. Close observation of the potential long-term effects of NDMA-contaminated valsartan seems advisable.

The angiotensin II receptor antagonist valsartan is used predominantly to treat hypertension and heart failure (1, 2, 3, 4). In 2018, N-nitrosodimethylamine (NDMA) was detected in the valsartan active substance manufactured by Zhejiang Pharmaceuticals (5,6). Preparations containing the contaminated valsartan were withdrawn from the market by regulatory agencies across the world (5,7). In Germany, the Federal Institute for Drugs and Medical Devices (BfArM) ordered the recall of drug products contaminated with NDMA in July 2018. The NDMA contamination seems to be the result of a change in the manufacturing process in 2012 (8). Thus, patients may have been exposed to contaminated valsartan from 2012 until the recall. Investigations of other sartans with a tetrazole ring structure have revealed contamination with no more than small amounts of NDMA in only a few cases. NDMA is one of the most potent mutagenic carcinogens in animal models and was classified by the International Agency for Research on Cancer (IARC) as probably carcinogenic to humans (9, 10, 11).

A Danish cohort study based on healthcare system registry data reported no statistically significantly elevated overall risk of cancer and no increase in the risk of some individual cancers after exposure to drug products containing NDMA-contaminated valsartan (12). However, the sample size of the Danish study was limited to a total of 5150 patients, which may explain the non-significance of the results (12). For our cohort study we used a large longitudinal sample from the AOK, a large German statutory health insurance fund. We examined the association between filled

prescriptions of potentially NDMA-contaminated valsartan drug product prescription and cancer risk in comparison with non-contaminated valsartan. Our results provide insights based on a substantially higher number of patients than in the Danish study. We also focus on various cancer outcomes with a large number of cancer events.

Methods

The *Figure* provides an overview of the study design. The data set comprises health insurance data from the AOK. It includes all patients aged 40 years or older at the beginning of 2012 who filled at least one prescription of valsartan between 1 January 2012 and 31 December 2017. Potential NDMA contamination was assessed on the basis of the pharmaceutical registration number (PZN) as product identifier in the filled prescription records and information on valsartan drug products from marketing authorization holders. The outcome was an incident cancer diagnosis. Cox regression models with time-varying variables and adjustment for potential influencing factors were used to calculate hazard ratios (HR) for cancer overall and for several individual cancer types. Detailed information can be found in the *eMethods*.

Figure
Overview of the study design

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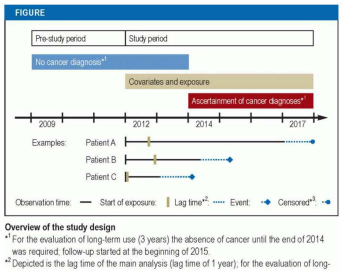

Overview of the study design
*1 For the evaluation of long-term use (3 years) the absence of cancer until the end of 2014 was required; follow-up started at the beginning of 2015.
*2 Depicted is the lag time of the main analysis (lag time of 1 year); for the evaluation of long-

Results

The study cohort comprised 780 871 persons with a filled valsartan prescription during the period 2012–2017. Of these, 409 183 were classified as ever and 371 688 as never exposed to potentially NDMA-contaminated valsartan. The characteristics of the study cohort in 2012 are presented in *Table 1*. The mean and median person-times were 3.1 years (standard deviation 1.5 years) and 3.25 years (interquartile range 2–4.75), respectively.

Table 1
Baseline characteristics of the study cohort

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TABLE 1
Baseline characteristics of the study cohort

Characteristic		All (N = 780 871) (%)	NDMA exposure: Not exposed (n = 371 688) (%)	NDMA exposure: Exposed (n = 409 183) (%)
Gender	Male	312 146 (40.0)	156 360 (42.1)	155 786 (38.1)
	Female	468 725 (60.0)	215 328 (57.9)	253 397 (61.9)
Age: median (IQR)		68 (57–75)	66 (55–74)	69 (58–76)
Prevalent use	No	534 519 (68.5)	300 370 (80.8)	234 149 (57.2)
	Yes	246 352 (31.5)	71 318 (19.2)	175 034 (42.8)
SSRI		36 825 (4.7)	16 202 (4.4)	20 623 (5.0)
NSAID		316 350 (40.5)	150 730 (40.6)	165 620 (40.5)
5α-Reductase inhibitors		6136 (0.8)	2684 (0.7)	3452 (0.8)
Low-dose ASA		94 061 (12.0)	38 988 (10.5)	55 073 (13.5)
Statins		237 998 (30.5)	102 502 (27.6)	135 496 (33.1)

For the outcome cancer overall, exposure to potentially NDMA-contaminated valsartan was not associated with an increased risk of an incident cancer diagnosis in comparison with exposure to non-contaminated valsartan (adjusted HR 1.00, 95% confidence interval [0.98; 1.02]; *eTable 1*). A similar result was obtained after adjustment for age and gender only (HR 1.01 [0.99; 1.03]). Based on the manufacturers' information about the packages of valsartan drug products sold, we were able to classify the filled valsartan prescriptions into different degrees of likelihood of contamination, from possibly to probably contaminated with NDMA *(eMethods)*. Exposure to neither possibly (adjusted HR 1.00 [0.97; 1.03]; *eTable 1*) nor probably (adjusted HR 0.99 [0.97; 1.02]; *eTable 1*) NDMA-contaminated valsartan was associated with the endpoint cancer overall. Differentiation between prevalent and incident exposure to potentially NDMA-contaminated valsartan showed no association with the endpoint cancer overall in either case (adjusted HR 0.97 [0.94; 1.01] and adjusted HR 1.01 [0.98 to 1.04], respectively; *eTable 1*). Higher exposure to potentially NDMA-contaminated valsartan, based on defined daily doses (DDDs), had no effect on the overall cancer rate *(eTable 1)*. For sensitivity analyses, the lag time between the last quarter assessed for exposure status and the initial cancer diagnosis or the end of the person-time was varied from 6 months to 2 years. We observed no significant

differences across this lag time spectrum *(eTable 2)*. In a separate analysis we examined long-term use of valsartan, defined as filling of valsartan prescriptions in at least nine quarters of the first 3 years of the study period. Long-term use showed no association with the change in overall cancer rate (adjusted HR 0.96 [0.89; 1.04]); neither were dose-dependent effects observed *(eTable 1)*.

Table 2
Liver cancer risk due to use of potentially NDMA-contaminated valsartan drug products compared with uncontaminated valsartan

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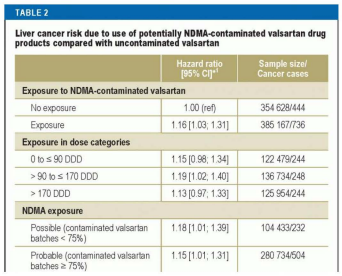

TABLE 2

Liver cancer risk due to use of potentially NDMA-contaminated valsartan drug products compared with uncontaminated valsartan

	Hazard ratio [95% CI][a1]	Sample size/ Cancer cases
Exposure to NDMA-contaminated valsartan		
No exposure	1.00 (ref)	354 628/444
Exposure	1.16 [1.03; 1.31]	385 167/736
Exposure in dose categories		
0 to ≤ 90 DDD	1.15 [0.98; 1.34]	122 479/244
> 90 to ≤ 170 DDD	1.19 [1.02; 1.40]	136 734/248
> 170 DDD	1.13 [0.97; 1.33]	125 954/244
NDMA exposure		
Possible (contaminated valsartan batches < 75%)	1.18 [1.01; 1.39]	104 433/232
Probable (contaminated valsartan batches ≥ 75%)	1.15 [1.01; 1.31]	280 734/504

eTable 1
Overall cancer risk from use of potentially NDMA-contaminated valsartan drug products compared with uncontaminated valsartan

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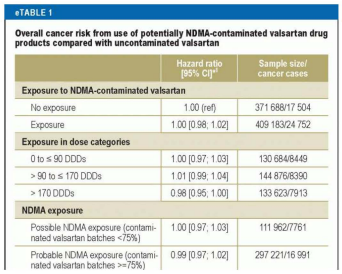

eTABLE 1

Overall cancer risk from use of potentially NDMA-contaminated valsartan drug products compared with uncontaminated valsartan

	Hazard ratio [95% CI][a1]	Sample size/ cancer cases
Exposure to NDMA-contaminated valsartan		
No exposure	1.00 (ref)	371 688/17 504
Exposure	1.00 [0.98; 1.02]	409 183/24 752
Exposure in dose categories		
0 to ≤ 90 DDDs	1.00 [0.97; 1.03]	130 684/8449
> 90 to ≤ 170 DDDs	1.01 [0.99; 1.04]	144 876/8390
> 170 DDDs	0.98 [0.95; 1.00]	133 623/7913
NDMA exposure		
Possible NDMA exposure (contaminated valsartan batches <75%)	1.00 [0.97; 1.03]	111 962/7761
Probable NDMA exposure (contaminated valsartan batches >=75%)	0.99 [0.97; 1.02]	297 221/16 991

eTable 2
Overall cancer risk and liver cancer risk from use of potentially NDMAcontaminated valsartan drug products compared with uncontaminated valsartan, different lag times

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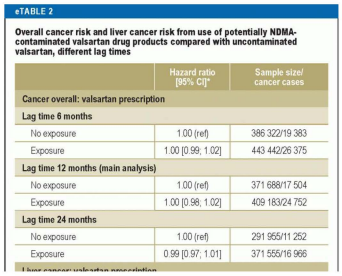

eTABLE 2

Overall cancer risk and liver cancer risk from use of potentially NDMA-contaminated valsartan drug products compared with uncontaminated valsartan, different lag times

	Hazard ratio [95% CI][a]	Sample size/ cancer cases
Cancer overall: valsartan prescription		
Lag time 6 months		
No exposure	1.00 (ref)	386 322/19 383
Exposure	1.00 [0.99; 1.02]	443 442/26 375
Lag time 12 months (main analysis)		
No exposure	1.00 (ref)	371 688/17 504
Exposure	1.00 [0.98; 1.02]	409 183/24 752
Lag time 24 months		
No exposure	1.00 (ref)	291 955/11 252
Exposure	0.99 [0.97; 1.01]	371 555/16 966

The analysis of individual cancer types showed a significant association between potentially NDMA-contaminated valsartan and liver cancer (adjusted HR 1.16 [1.03; 1.31], p = 0.017; *Table 2*). No association with potentially NDMA-contaminated valsartan exposure was detected for any other cancer outcomes *(Table 3)*. The association with liver cancer remained stable after basic adjustment for age and gender (HR 1.20 [1.06; 1.35]) and also after additional adjustment for hepatitis (ICD-10 codes B15–B19) and other liver diseases (ICD-10 codes K70–K76, Z944). Following correction for age and gender there was an increase from 34.6 to 39.1 per 100 000 person-years in the incidence rate of liver cancer for the valsartan-exposed population above 40 years of age according to the 2011 German census. However, no dose-dependent effect on the risk of liver cancer was found for higher exposure to potentially NDMA-contaminated valsartan *(Table 2)*. Varying lag times of 6 months to 2 years also did not alter the effect *(eTable 2)*. Evaluation of 3-year long-term use of potentially NDMA-contaminated valsartan resulted in a decreased sample size (75 112 patients, 130 cases of liver cancer) and showed no significant association with liver cancer (adjusted HR 1.22 [0.80; 1.89]; *Table 2*). The incidence rates for exposure and no exposure are given in *eTable 1* and *Table 2*.

Table 3

Risk of individual cancers owing to use of potentially NDMA-contaminated valsartan drug products compared with uncontaminated valsartan

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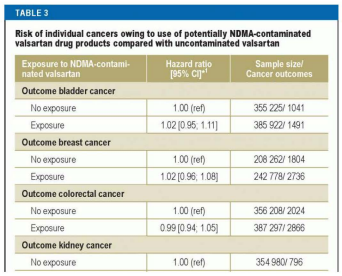

TABLE 3

Risk of individual cancers owing to use of potentially NDMA-contaminated valsartan drug products compared with uncontaminated valsartan

Exposure to NDMA-contaminated valsartan	Hazard ratio [95% CI][1]	Sample size/ Cancer outcomes
Outcome bladder cancer		
No exposure	1.00 (ref)	355 225/ 1041
Exposure	1.02 [0.95; 1.11]	385 922/ 1491
Outcome breast cancer		
No exposure	1.00 (ref)	208 262/ 1804
Exposure	1.02 [0.96; 1.08]	242 778/ 2736
Outcome colorectal cancer		
No exposure	1.00 (ref)	356 208/ 2024
Exposure	0.99 [0.94; 1.05]	387 297/ 2866
Outcome kidney cancer		
No exposure	1.00 (ref)	354 980/ 796

Discussion

In our study we observed a slight elevation in the risk of liver cancer with the use of potentially NDMA-contaminated valsartan. Our analysis is based on a large longitudinal data set from a large statutory health insurance provider and on detailed information about potentially NDMA-contaminated valsartan from the marketing authorization holders of valsartan drug products.

Comparison with other studies on valsartan exposure

Only one cohort study on this topic has been published to date (12); the Danish registry study by Pottegard et al. has only a small sample size, comprising 5150 persons with prescription of valsartan. Our study contains around 150 times more persons with valsartan prescription. Pottegard et al. examined effects on the overall cancer rate and individual cancers, finding no statistically significant associations (HR for cancer overall 1.09 [0.85; 1.41] (12). However, the number of cancer cases in the Danish study was limited (302 cancers overall; only eight cases each of kidney and bladder cancer). The statistical power for detection of small effects is therefore limited, and no precise statements on small effect sizes can be made. With regard to qualitative effects, our findings are in agreement with the Danish study, as we detected no modification of cancer risk by potentially NDMA-contaminated valsartan for cancer overall or for the individual cancer types examined by the Danish authors.

For liver cancer, however, we observed a statistically significant association. This is interesting, as from a biological perspective liver cancer is the most likely form of cancer to resulting from NDMA contamination. That is the reason why we classified the occurrence of liver cancer as an independent primary endpoint compared with other specific types of cancer. Pottegard et al. did not report results for liver cancer, because no cases of liver cancer were detected among the persons who had received potentially NDMA-contaminated valsartan in the Danish study (12).

Strengths and limitations of the study

The main strength of our study is the cohort size of 780 871 persons with valsartan prescription and longitudinal health insurance claims data information from 2009 to 2017, drawn from the almost one third of the German population insured by the AOK (13, 14). This allowed us to perform analyses in an unselected patient population in a r ation from t aceuticals a This e n G

14. Bundesgesundheitsministerium: Gesetzliche Krankenversicherung. Mitglieder, mitversicherte Angehörige und Krankenstand,Jahresdurchschnitt 2019. www.bundesgesundheitsministerium.de/fileadmin/Dateien/3_Downloads/Statistiken/GKV/Mitglieder_Versicherte/KM (last accessed on 8 March 2021).

The study also features limitations. Because the study is based on observational health insurance claims data (i.e., on non-randomized data), we cannot rule out residual confounding. Although we adjusted our analysis by including numerous potential influencing factors, some risk factors for cancer, such as smoking habits, nutritional habits, and genetic predisposition, are not available in routine health insurance data and, therefore, could not be integrated into the analysis. Nevertheless, the frequency of unmeasured cancer risk factors should be similar in the NDMA-exposed and non-exposed groups. However, we cannot rule out unmeasured confounders such as group differences in adherence patterns, due for instance to polypharmacy or differences in the Charlson comorbidity index. Inclusion of prevalent users did not alter the result. We detected only marginal differences between results with basic adjustment for age and gender and the fully adjusted model with all covariates. This indicates that the potentially influential factors included

in the model had no strong effects. Although detailed batch/use information on potentially NDMA-contaminated valsartan was provided, we had no information on the exact NDMA content of individual valsartan tablets. However, sensitivity analyses with varying degrees of possible or probable NDMA contamination yielded results comparable to those of the main analysis. A further limitation is that due to the limited follow-up time we were not able to monitor the long-term effects of NDMA-contaminated valsartan for more than 3 years.

Biological background

NDMA is classified by the IARC as probably carcinogenic (group 2A). It is carcinogenic in the tissues of experimental animal species with metabolism similar to that of human tissues (9, 15). Ingested NDMA is metabolized by cytochrome P450-dependent mixed-function oxidases to methyldiazonium ions, which alkylate proteins, DNA, and RNA (16, 17, 18, 19). In experimental animals oral NDMA exposure increases tumor incidences in various organs, predominantly in the liver (19). Those effects become measurable at doses of about 10 µg/kg/day (19). In our study, exposure to NDMA elevated liver cancer risk independent of dose. This might support the hypothesis of a threshold dose for the development of cancer. NDMA can be found among other N-nitroso compounds in foods, especially those that are smoked or dried at high temperature (20). Epidemiological studies investigating the association between explicit dietary NDMA exposure and cancer yielded inconclusive results (21, 22, 23). No inferential statistical analyses were available on the association between human NDMA exposure and liver cancer. Nevertheless, exposure to NDMA-rich food in regions with high liver cancer rates in Thailand could potentially be based on a correlation, although no conclusive studies have been published (24). The observed rates of cancer overall and liver cancer in our study were around 1.5–2 times the national average. This is most likely due to the inclusion of persons aged 40 years and older for analysis, resulting in a study population older than the general population. The effect of NDMA exposure on liver cancer is a statistical result. However, molecular mechanisms known for NDMA in the pathogenesis of liver cancer in experimental animals support an association with NDMA exposure in humans. It may be that NDMA exposure promotes cancer development in already existing, as yet undiagnosed early stages and thus hastens clinical manifestation.

Regulatory and public health implications

Our study provides information for regulatory authorities worldwide to assess the public health impact of NDMA contamination in valsartan drug products. It is an example of how extensive real-world data from statutory health insurance funds can be used to examine urgent drug safety questions with pharmacoepidemiological methods. The immediate recall of all potentially NDMA-contaminated valsartan drug products by regulatory authorities worldwide was necessary in order to protect public health. The detection of different nitrosamine impurities in drug products since 2018 led to the introduction of a new threshold by the European Medicines Agency (25).

eTable 3
ATC codes and ICD-10 codes

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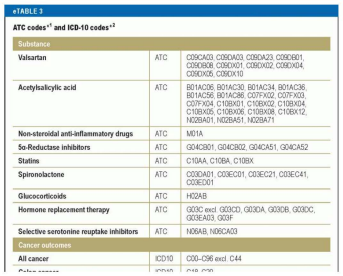
eTABLE 3
ATC codes[1] and ICD-10 codes[2]

Substance		
Valsartan	ATC	C09CA03, C09DA03, C09DA23, C09DB01, C09DB08, C09DX01, C09DX02, C09DX04, C09DX05, C09DX10
Acetylsalicylic acid	ATC	B01AC06, B01AC30, B01AC34, B01AC56, B01AC56, B01AC86, C07FX02, C07FX03, C07FX04, C10BX01, C10BX02, C10BX04, C10BX05, C10BX06, C10BX08, C10BX12, N02BA01, N02BA51, N02BA71
Non-steroidal anti-inflammatory drugs	ATC	M01A
5α-Reductase inhibitors	ATC	G04CB01, G04CB02, G04CA51, G04CA52
Statins	ATC	C10AA, C10BA, C10BX
Spironolactone	ATC	C03DA01, C03EC01, C03EC21, C03EC41, C03ED01
Glucocorticoids	ATC	H02AB
Hormone replacement therapy	ATC	G03C excl. G03CD, G03DA, G03DB, G03DC, G03E A03, G03F
Selective serotonine reuptake inhibitors	ATC	N06AB, N06CA03
Cancer outcomes		
All cancer	ICD10	C00–C96 excl. C44

Conclusion

We examined the association of NDMA-contaminated valsartan drug products and cancer risk in a large health insurance data set including more than 780 000 persons. We detected a small, yet statistically significant increase in the risk for liver cancer with the use of NDMA-contaminated valsartan while no association was found for overall cancer risk or other examined single cancer outcomes. However, the present study can only state the existence of a statistical association. Causality cannot be inferred. Long-term effects of regular use of potentially NDMA-contaminated

valsartan for more than 3 years could not be evaluated because of the currently still relatively short follow-up time. Therefore, careful monitoring of potential further effects of NDMA-contaminated valsartan after longer periods is advisable.

eFigure

Overview of study cohort after application of the selection and data quality control criteria

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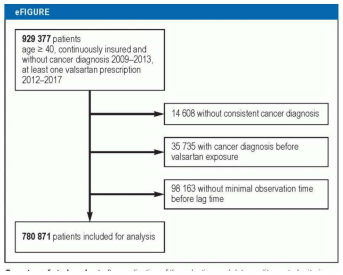

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Data sharing statement

The data cannot be shared with or transmitted to third parties due to legal restrictions.

Conflict of interest statement

The authors declare that no conflict of interest exists.

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►Supplementary material

eReferences, eMethods, eTables, eFigure:

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